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TWO YEAR ORAL (DIET) TOXICITY / CARCINOGENICITY STUDY OF FLUOROCHEMICAL FC-143 IN RATS

(RIKER EXPERIMENT NO. 0281CR0012)

VOLUME 1 OF 4

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TWO YEAR ORAL (DIET) TOXICITY/CARCINOGENICITY STUDY OF FLUOROCHEMICAL FC-143 IN RATS

(RIKER Experiment No. 0281CR0012)

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TWO YEAR ORAL (DIET) TOXICITY/ONCOGENICITY STUDY OF FLUOROCARBON FC-143 IN RATS

(RIKER Experiment No. 0281CR0012)

REPORT SUMMARY

The purpose of this study was to assess the potential toxicity and oncogenicity of FC-143 (ammonium perfluoroalkyl carboxylate) mixed in the diet and fed to 50 rats per sex per group for two years. An interim sacrifice and evaluation was performed at one year on 15 additional rats per sex from the control and high-dose groups.

A total of 360 Sprague-Dawley male and female rats were assigned to three experimental groups. The FC-143-treated groups were fed diets containing either 300 or 30 ppm of FC-143 for two years, while a control group received only untreated feed.

In-life observations performed during the course of the study included: daily observations for abnormal signs; periodic physical examinations; body weight and feed consumption; ophthalmoscopic examinations; and clinical pathology including hematology, clinical chemistry and urinalysis.

Macroscopic postmortem examinations were performed on all animals that died or were terminated prior to the end of the scheduled dosing. Selected organ weights were obtained from all of the rats necropsied at 1 year as well as from 15 rats/sex/group, randomly selected from the control and both FC-143-treated groups, at the termination of the study. Selected tissue specimens were harvested from each animal at necropsy, and preserved for future histopathologic examination. Microscopic evaluation was performed on all tissues saved from all of the control and high-dose rats, while a similar evaluation was performed on a modified list of tissues obtained from the low-dose animals.

The major in-life findings associated with FC-143 administration consisted of: a dose-related decrease in mean body weight and a treatment-related

increase in feed consumption per kilogram of mean body weight in males; and a slight treatment-related increase in the incidence of ataxia in the females. There was no increase in mortality in the high-dose treatment group when compared to similar values for the control population.

FC-143 related hematologic changes in both treated groups consisted of a decrease in red blood cell counts, hemoglobin concentration and hematocrit values at various times throughout the study. Generally, these hematology parameters remained within the acceptable ranges for the rat.

The primary FC-143 associated changes were found in the liver. These alterations were characterized by increased liver weights, hepatomegalocytosis with vacuolation of the cytoplasm, and some evidence of hepatocellular degeneration with occasional signs of necrosis. These liver changes were found early in the study and showed very little evidence of progression at the end of two years.

The incidence of almost all neoplasms in this study was relatively low, and the types and incidence of neoplasms were generally not different from those commonly found in geriatric Sprague-Dawley rats. Hepatocellular tumors were very slightly increased in the high-dose male rats. The other neoplasms in this study were associated with endocrine and/or endocrine-sensitive organs. The increased incidence of mammary or testicular tumors in the high- and low-dose groups was not statistically significant and/or was similar to the spontaneous incidence reported for Sprague-Dawley rats.

Under the conditions of this study and based on tumor incidence, types of tumors, time of tumor appearance, and the survival rate at two years, FC-143 is not considered to be carcinogenic in the rat.

TWO YEAR ORAL (DIET) TOXICITY - CARCINOGENICITY STUDY OF FLUOROCHEMICAL FC-143 IN RATS

INTRODUCTION

This study was designed to evaluate the chronic toxicologic and carcinogenic potential of FC-143, an industrial grade of ammonium perfluornalkyl carboxylate, in rats following oral administration in the diet for a period of two years. The study was sponsored by the Commercial Chemical Division of 3M Company and was performed by the Pathology and Toxicology Department of Riker Laboratories, Inc., 3M Company, St. Paul, Minnesota, U.S.A. The study and subsequent reporting was coordinated for the sponsor by the 3M Corporate Toxicology Services staff. The in-life or dosing portion of the study began on April 21, 1981, and was completed on May 5, 1983. A copy of the study protocol with amendments is contained in this report as Appendix Item H.

The study was designed to evaluate two separate fluorochemicals, FM-3924 and FC-143, using a common set of control animals. This report will describe the results of the FC-143 treatment while the results relating to the FM-3924 study will be reported separately.

The study was conducted in accordance with the Department's Standard Operating Procedures (ie., SOPs) and in compliance with the Food and Drug Administration's Good Laboratory Practice (GLP) regulations (21 CFR Part 58). Various phases of the study were inspected by the RIKER Quality Assurance Unit; their statement is presented in Appendix Item I of this report. The original signed protocol with amendments, list of study personnel, raw data, study specimens, and other pertinent study samples/documents will be maintained within the Pathology and Toxicology Department archives currently located at 3M Center in St. Paul, Minnesota.

MATERIALS AND METHODS

Test System: Three-hundred and sixty Sprague-Dawley rats [Crl:COBS® CD(SD)BR, Charles River, Portage, MI], 39 to 41 days of age when treatment began, were divided by means of a table of random numbers into three groups. The control and high-dose groups each contained 65 males and 65 females, whereas the low-dose group contained 50 male and 50 female rats.

The rats were housed in hanging stainless steel cages with wire mesh floors and fronts. The males were housed individually, but the females were housed two per cage. The control animals were housed in separate rooms from those which received FC-143 in order to prevent a possible cross contamination by potential vaporization and/or sublimation of the test article which has a finite vapor pressure at room temperature. Air samples were taken from each of the animal treatment rooms four months after the initiation of the study in order to assay for the presence of airborne contaminants. The samples were analyzed by the Analytical Section of the 3M Central Research Laboratory and were found to be below detectable limits for the suspected fluorochemicals. In addition to the air monitoring, 30 untreated sentinel rats were placed in each of the two animal rooms. From each animal room, 5 male and 5 female sentinel rats were euthanized during the first week of the study, and at 1 and 3 months after the start of the study. Plasma samples obtained from these rats were analyzed for organic fluorine and were found to contain less than one part per million (see Appendix Item A).

Each animal room was temperature and humidity controlled with the lighting on a 12 hour light/dark cycle. Individual rats were uniquely identified by an animal number on a cage card and on a tag affixed to their ear. Feed (Certified Purina Laboratory Chow, Ralston-Purina Co., St. Louis, MO) and tap water were provided ad libitum.

Test Substance/Diet Preparation: FC-143 (Lot 37) was analyzed by the Commercial Chemicals Divisions (CCD) Analytical Laboratory prior to the start of the study, after approximately one year from the start of the study, and at the termination of the dosing period. No detectable changes were found in the test substance during this time (see CCD Analytical Reports Nos. 308, 348 and 413 in Appendix Item J).

The test substance was a white powder which was added (ie, stratified) directly into an appropriate quantity of untreated diet and mixed in a Hobart^{R} blender for approximately 20 minutes for each separate batch. Prior to initiating compound administration to any animals, the test substance/diet mixture was assayed. FC-143 was found to be uniformly blended and stable for one to two weeks in the ground feed (see CCD Analytical Report No. 209 in Appendix Item J).

Test article/diet mixtures were prepared fresh weekly during the study and representative samples of each were collected and assayed for test article content and homogeneity during the first month of the study and at 3 month intervals thereafter (see Appendix Item B). The results of these assays indicated that the level of FC-143 was generally within a few percent of that desired (Table 1).

The rats received either FC-143 treated or control (ie, untreated) diets in glass jars 10.2 cm high x 8.9 cm in diameter. A 5.1 cm access hole was cut in the stainless steel lid. On a weekly basis the diet jars were removed and replaced with clean jars containing fresh diet mixtures.

Experimental Design: The study consisted of one control group and two treatment groups. The dosage levels and animal distribution are listed hereinafter.

Treatment Groups	Dosage Levels (ppm)	Group Size & Animal Numbers	
		Males (An. Nos.)	Females (An. Nos.)
1 - Control	0	65 (3516-3580)	65 (4576-4640)
5 - High	300	65 (3581-3645)	65 (4641-4705)
6 - Low	30	50 (3646-3695)	50 (4706-4755)

An interim termination at one year involved 15 male and 15 female rats from both the control and high-dose groups. The remaining 50 animals per sex per group continued on study.

In-Life Observations: All animals were observed daily throughout the two year dosing period. Weekly physical examinations included palpation for the presence of masses as well as observations for pharmacotoxic signs; mortality was recorded daily. During the study, moribund animals were closely monitored, and euthanized when in the judgement of the Study Director death appeared to be imminent in order to harvest non-autolysed tissue for subsequent histopathologic examination.

Body weights and feed consumption were recorded once per week for the first six months, and then once every two weeks for the remainder of the study.

Eye examinations using indirect ophthalmoscopy and/or slit lamp biomicroscopy were performed on the control and high-dose rats by the Staff Veterinarian prior to compound administration and at approximately one year. The eyes of the surviving control and high-dose animals were examined 2-3 weeks prior to the termination of the study by a consulting Veterinary Ophthalmologist (see Appendix Item G).

Clinical pathology determinations included hematology, clinical (serum) chemistry and urinalysis. Tests were conducted on samples obtained from 15 rats per sex from each group at 3, 6, 12, 18 and 24 months; animals were randomly selected at each time interval. Hematologic tests included total red and white blood cell counts, hemoglobin, hematocrit, and a differential white blood cell count. Clinical chemistry parameters included total bilirubin, total protein, albumin, blood urea nitrogen (BUN), glucose, alkaline phosphatase (AP), creatine phosphokinase (CPK), aspartate aminotransferase (AST-formerly known as SGOT), alanine aminotransferase (ALT-formerly SGPT), and calcium. Urine tests included pH, specific gravity, albumin, glucose, bilirubin, occult blood and ketones.

Blood samples were collected from the retrobulbar venous plexus of anesthetized rats which had been fasted overnight. Blood was generally collected from the right eye. Urine samples were obtained by placing each rat in an individual metabolism cage for 20-22 hours. The specific methods

used for hematology, clinical chemistry and urinalysis are outlined in Appendix C. The mean hematology and clinical chemistry values from the treated groups were compared to both the concurrent control group as well as normal ranges for these parameters obtained from historical control animal data generated in this laboratory (Appendix C).

Metabolic Examination: Overnight (ie, about 24 hour) urine and fecal samples were collected at 2, 5, 11 and 23 months from five rats per sex per group for total organic fluoride analysis, and for the presence of FC-143. At the scheduled one and two year necropsies, samples of liver, blood, kidney, spleen, lung and bone marrow (ie, from the femur) were saved from five rats/sex/group. After collection, all specimens were frozen pending subsequent analysis by the RIKER Drug Metabolism Department.

Once these specimens are analyzed, a separate report regarding this experimental work will be prepared by the Drug Metabolism department.

Postmortem Examinations: Gross postmortem examinations were performed on all rats which died during the study and those which were terminated at the one year interim and two year necropsies. At necropsy, an examination was made of the external body surface and body orifices. The carcass was then opened and the contents of the abdomen, thorax and cranium were examined <u>in situ</u> and following removal from the body.

Organ weights (ie, wet tissue) were obtained at the interim termination from both the control and high-dose groups, and from the control and both FC-143 treated groups at the two year necropsy. The weights of the adrenal glands, brain, testes, heart, kidneys, liver, spleen and uterus were recorded for 15 randomly selected rats/sex/group. Body weights were obtained just prior to necropsy from the same rats in order to calculate organ weights relative to whole body weights.

Representative samples of the following tissues and organs from each rat were fixed in 10% neutral, buffered formalin for subsequent histologic processing:

Aorta
Adrenals (2)
Brain (3 Sections including
Liver (2 Sections)
Lung (2 Sections)
Lymph node (mesenteric)

frontal cortex and basal ganglia, parietal cortex and thalamus; cerebellum and pons)
Eyes
Gonads
Ovaries (2)
Testes/Epididymides (2)
Heart
Small Intestine (3 Sections)
Large Intestine
Kidneys (2 Sections)
Mammary Gland (females)
Pancreas
Pituitary
Salivary Gland
Spinal Cord/Bone Marrow (vertebrae)
Spleen
Stomach
Thyroid/Parathyroid/Trachea/Esophagus
Urinary Bladder
Uterus or Prostate
Any tissue masses (suspected tumors)
Any gross lesion

Light microscopic examination was performed on hematoxylin and eosin stained, paraffin-embedded tissue sections from all tissues listed above, when available, and from all rats in the control (Group 1) and high-dose (Group 5) populations regardless of the cause of death. Microscopic examination of tissues from the low-dose (Group 6) rats included the tissues listed above except: aorta, brain, eyes, small and large intestines, lymph node(s), and spinal cord/bone marrow. The histopathologic examination and evaluation of these tissues was performed by Dr. Robert G. Geil, consulting Veterinary Pathologist (see Appendix Item D).

Biostatistical Methods: The means and standard deviations for body weights, feed consumption, absolute organ weight, relative organ weight to whole body weight, organ weight to brain weight ratios and other laboratory data were determined separately for each sex and dose group.

These data were analyzed using Bartlett's test for homogeneity of variance. If this test was not significant at alpha = 0.001, the data were further analyzed by comparing each treated group to the control group using a two-tailed Dunnett's test at the alpha = 0.05 significance level. The results of Dunnett's test have been indicated by asterisks on the mean tables. If Bartlett's test was significant at alpha = 0.001, the data were ranked and a two-tailed Dunnett's test was performed on the ranks. These results have been indicated by the pound sign (#) on the mean tables.

In addition, for each organ/lesion classification the sexes were analyzed separately using a two-tailed Fisher's Exact Test comparing each treated group to the controls. An alpha = 0.05 significance level with Bonferroni's adjustment for multiple comparisons was used within each organ/lesion/sex category. If the expected value of each cell was greater than 20, then Yates' corrected Chi-Square test was used. An asterisk on the summary tables indicates a significant difference between the controls and the treated group.

Internal RIKER memoranda pertaining to these biostatistical procedures are presented within Appendix Item E.

RESULTS

In-Life Findings: Body weight gains were depressed in excess of 10% in the FC-143 high-dose males compared to the control males through 66 weeks of the study. There was an approxi..ate 21% decrease in the high-dose body weights by week 6. This difference was statistically significant from week 2 of the study until week 98 when the high-dose and control male body weights had gradually equalized. Likewise in the low-dose male group, a 5% decrease in body weights was observed at week 6, however, there was little additional decrease thereafter (Table 2, Figure 1 and Appendix F). The occurrence of a mild SDA virus outbreak at different times during the study may have had a slight influence on the body weight data (see p. 12).

Mean body weights were only very slightly decreased in the FC-143-treated females compared to the control female values through the first 18 months of the study. At 18 months, there was a gradual decrease in mean body weights of high-dose females that reached a maximum of -11% at 92 weeks. The low-dose females also showed a decreased body weight, but the effect was not statistically significant and the change was of a much lower magnitude (Table 3, Figure 2 and Appendix F).

Mean feed consumption, presented as grams of diet consumed per day per kilogram of mean body weight, was increased in all of the FC-143-treated males throughout the study when compared to the male control feed consumption. This change was more pronounced in the high dose group where there was roughly a 13% increase noted with sporadic values going as high as 29% during the two year test period. In the females the pattern was less consistent, but there was a trend toward lowered feed consumption in both FC-143-treated groups compared to the female control values (Tables 4 and 5 and Figures 3 and 4). Overall, these variations were related to the variation of body weight among groups.

Actual mean feed consumption (without regard for body weight change) was slightly decreased in the high-dose males relative to control males, for the first year of the study. Feed consumption in low-dose males, while somewhat inconsistent, was slightly increased during this same period.

During the second year, the feed consumption of both FC-143-treated male groups was reasonably stable and consumption was comparable to that of the control group. All of the treated female groups tended to consume less feed than the comparable controls throughout the study. The greatest decreases occurred from 18 months to termination with the high- and low-dose groups being equally affected (Table 6 and 7 and Appendix F).

The test article concentration measured as parts per million in the diet was determined at 3 month intervals with a duplicate analysis performed when aberrant values were detected. The mean deviations from the target concentration of the high- and low-dose FC-143 groups were less than 3% (Table 1).

Actual test article consumption was determined for each 2 week period for each sex and each experimental group, and expressed as mg/kg/day. The mean test article consumption was estimated to be: males, 14.2 and 1.3 mg/kg/day; females 16.1 and 1.6 mg/kg/day for the high- and low-dose groups, respectively. Mean test article consumption values calculated at 2 week intervals for the entire study are presented in Table 8.

Overall survival rates for the FC-143-treated rats were good during the full two years of the test period. There were fewer deaths recorded in the high-dose males and females than in the comparable control populations. At the end of 1 year, 15 rats/sex from the control and high-dose groups were terminated to fulfill the protocol requirement for the interim sacrifice. The final survival rate then based on 50 rats/sex/group at the end of 104 weeks was: males, 70%, 88% and 72%; and females, 50%, 58% and 48% for the control, high- and low-dose groups, respectively. The increased survival rate observed in the high-dose male rats compared to the control male rats, was statistically significant ($p \leq 0.05$). Monthly mortality data are presented in Table 9.

A summary of the most commonly seen clinical signs is contained in Table 10. The only clinical sign that occurred more frequently in the test article-treated groups was a dose-related increase in ataxia reported for the FC-143- treated females. While the ataxia was most commonly associated

with morbid animals and was seen in the control males and females, only the treated females showed an increase in the incidence of this clinical sign; 2, 15 and 9 cases in the control, high- and low-dose groups, respectively. The incidences of all other clinical signs in the FC-143-treated groups were generally less than or equal to the incidence of the same signs in the control group.

Rats administered the test article experienced a suspected outbreak of sialodacryoadenitis (SDA) viral infection between the first and second months of the study. Clinical signs included swollen submandibular salivary glands and occasional ocular manifestations. The submandibular swelling was resolved within 10 days, and the incidence of ocular changes was extremely low. Similarly, the control animals had comparable symptoms during the sixteenth month of the study. Thirteen males and 13 females in the control group demonstrated signs of this condition which lasted for about 16 days from the time of onset. One male and 3 females developed ocular opacities during this period.

The incidence of palpable tissue masses in FC-143-treated groups was comparable to that of the control group. There were more animals with masses in the male controls than in the male treated groups; that is, 19, 10 and 7 animals in the control, high- and low-dose groups, respectively. Likewise, when the number of palpable masses which regressed or resolved before the termination of the experimental period were evaluated, there were still fewer masses found in the FC-143-treated animals than in the control group (Table 10).

The results of the final ophthalmoscopic examinations were negative relative to any FC-143 treatment-related effects. Changes that were observed included a random distribution of cataracts believed to be normal geriatric changes of the lens and some cases of chronic uveitis and superficial keratitis which were also considered to be within normal limits for aging populations of rats (Table 11 and Appendix G). Many of the rats found to have ocular lesions were identified as rats which were used to obtain blood samples via the retrobulbar venous plexus.

Red blood cell counts, hemoglobin and hematocrit values were minimally decreased in the high-dose male rats compared to control values, from 3 through 18 months. Statistically significant ($p = <0.05$) decreases were seen at various times in the following parameters: erythrocytes at 6, 12 and 18 months; hemoglobin, 3 and 18 months; and hematocrit at 3, 12 and 18 months. While some of these parameters were also altered in the low-dose males, the changes were of a lesser magnitude and in some cases, were increased as well as decreased (Table 12). The female high-dose erythrocyte counts and hematocrits were slightly decreased at 3 months, but were slightly increased at 6 months compared to control values. At 12 months there was a statistically significant decrease in erythrocyte count, hemoglobin, and hematocrit (Table 13).

Mean leucocyte counts were increased in both male treatment groups compared to control values, through the first year of the study. These changes were due to increases in absolute counts of lymphocytes at 3 and 6 months, and in neutrophils at 12 months. Statistically significant increases were observed: in lymphocyte counts at 3 months in the high- and low-dose groups, and at 6 and 18 months in the low-dose group; and in neutrophil counts at 12 months in both groups (Table 12). Similar changes were not seen in the FC-143-treated females with the exception of a slight increase in neutrophils and a slight decrease in lymphocytes seen in the low-dose group at 18 months (Table 13).

Clinical chemistry findings at 3 months included slight increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (AP), as well as a moderate decrease in creatine phosphokinase (CPK) in both FC-143- treated male groups. From 6 until 18 months, the high- and low-dose male ALT, AST and AP values were increased above the concurrent control values, whereas these values in the high-dose group were still elevated at 24 months. Albumin values remained very slightly elevated in the high-dose males until the end of the study. Similar changes in clinical chemistry were not observed in the FC-143-treated female groups (Tables 14 and 15).

Urinary findings included increases in incidence and severity of albumin and occult blood in all of the male and female control and FC-143-treated groups at 12, 18, and 24 months. These findings were more pronounced in the males than in the females at the termination of the study. Other than an occasional incident of slight ketonuria in both control and FC-143-treated animals, there were no other remarkable urinary findings (Table 16).

Postmortem Findings: The Consulting Pathologist's complete report is located in Appendix D. The gross pathology findings seen at the 1 year interim sacrifice were unremarkable with the possible exception of a single high-dose male having small testes and 3/15 high-dose females with mammary masses compared to an incidence of 1/15 in control female rats.

Possible FC-143-related gross findings seen in male and female high-dose rats which were either found dead, euthanized in extremis, or euthanized at the termination of the study, included liver and testicular observations in the males and only a very slight increase in the incidence of mammary masses in the low-dose females. The liver findings seen in the males consisted of a slight increase in the incidence of liver masses, nodules and raised lesions, mottled livers and yellow or pale liver foci. While small testes were observed grossly in the control males as well as in both treated groups, testicular masses were found in 6/50 high-dose and 1/50 low-dose rats, but not in any of the controls. Mammary masses reported at necropsy in 1 high-dose and 2 low-dose males were found microscopically to be non-mammary lesions. Mammary masses were observed in 27/50, 26/50 and 37/50 of the control, high- and low-dose female rats, respectively. No remarkable FC-143-related liver changes were seen grossly in the female rats. Other gross pathologic findings were typical of findings in aging rats of this strain (Appendix D).

Organ weights presented as either absolute or relative (ratio of organ/body weight or organ/brain weight) values are contained in Tables 17 and 18. At the 1 year interim sacrifice where the only groups examined were the high-dose and controls (n = 15/sex/group), there was no change in male body weight (absolute) but a statistically significant ($p = <0.05$) increase in

relative liver and kidney weights (vs. body weight) for the FC-143-treated males only. At the terminal necropsy, slight increases in relative (organ vs. body weight) liver weights were noted for both the males and females of both dose groups, but the increases were not statistically significant. Slight increases in relative kidney weights were observed in both the male and female rats in the high-dose group; however, only in the females was this finding statistically significant.

Complete details of the histopathologic findings are contained in Appendix D and a summary of the major neoplastic and non-neoplastic microscopic changes found after 2 years of continuous oral administration of FC-143 are listed in Tables 19 and 20.

Histopathologic evaluation of the tissues from the animals necropsied at 1 year indicated the major FC-143 effects were confined to the liver. Diffuse hepatomegalocytosis (12/15 animals), hepatocellular necrosis (6/15 animals), and portal mononuclear cell infiltration (13/15 animals) were seen in the high-dose males while incidences in the control group were 0/15, 0/15 and 7/15, respectively. Testicular tubular atrophy with marked aspermatogenesis was found in 2/15 high-dose males but was absent in the control males. The only remarkable change seen in the high-dose females was minimal to mild hepatocellular vacuolation; the incidence for this finding was 11/15 at the high dose and 5/15 in the control group.

The majority of neoplasms observed after 2 years of dosing with FC-143, involved either the liver or one of several endocrine or endocrine-related organs (Table 19). Hepatocellular carcinomas were found in 6%, 10%, and 2% of the males from the control, high-, and low-dose groups, respectively. For the females, hepatocellular carcinomas were found only in the high-dose group with an incidence of 2%. The organ with the highest incidence of tumors was the pituitary gland where the incidences of adenomas in the males was 35%, 28% and 36%, and in the females at 71%, 71% and 83% for the control, high- and low-dose groups, respectively.

Mammary gland adenocarcinomas were present in both control and treated females at an incidence of 15%, 11% and 31% for the control, high- and

low-dose groups, respectively. In a similar comparison, fibroadenomas were seen in 22%, 48% and 42% of the female rats at the end of the study. Mammary gland adenomas (7%) and carcinomas (2%), were seen only in the female controls, while one high-dose female had a lymphangiosarcoma. An increase in testicular Leydig cell adenomas was statistically significant ($p = <0.05$) in the high-dose males. The incidence for this lesion was 0%, 14% and 4% in the control, high- and low-dose groups, respectively. There were minor variations in the tumor incidence patterns in the adrenals (pheochromocytomas) and thyroids which represent deviations in two commonly occurring spontaneous tumors of this strain of rat. Only the incidence of C-cell adenomas of the thyroid in male rats, appeared to show a slight dose dependent increase; namely, 0%, 9% and 4% for the control, high- and low-dose groups, respectively. However, C-cell carcinomas were seen only in the controls at an incidence of 5%.

Non-neoplastic changes were found at the termination of the study in the adrenals, heart, liver, lung, pancreas, ovaries, salivary glands, spleen, testes, thyroids and uterus (Table 20). As noted in the 1 year interim histopathologic evaluation, the liver was the primary organ associated with FC-143 treatment-related effects, and there was a remarkable consistency in the type of findings observed in the males after the second full year of test article administration. Megalocytosis, cystoid degeneration, and portal mononuclear cell infiltration were the major dose-related changes seen in both male and female test article-treated groups. Megalocytosis was found at an incidence of 0%, 80% and 12% in the males, and 0%, 16% and 2% in the females from the control, high- and low-dose groups, respectively. Hepatic cystoid degeneration, a condition characterized by areas of multilocular microcysts in the liver parenchyma, was more commonly seen in male rats with a control incidence of 8%, whereas the high- and low-dose males had incidences of 56% and 14%, respectively. The incidence of this lesion in females was 2% in both of the FC-143-treated groups. Hepatocellular necrosis was equally distributed between the control and FC-143-treated groups. The incidence of hyperplastic nodules, a localized proliferation of hepatic parenchymal cells, was slightly increased in the high dose groups with an incidence of 6% in the males and 2% in the females as compared to 0% and 2% in the control males and females, respectively.

No hyperplastic nodules were found in the low-dose group. The incidences of other hepatic changes such as basophilic hepatocyte alteration and/or chronic inflammatory changes consisting of portal mononuclear cell infiltration were slightly increased in the high-dose males, but only against a high incidence of similar changes in the control group.

Pulmonary changes that may be associated with the administration of FC-143 in the high-dose males, consisted of an increase in the incidence of alveolar macrophages (62%) and hemorrhage (44%) compared to control incidences of 20%. However, the incidence of chronic interstitial pneumonia and perivascular mononuclear infiltration was greatly reduced in the high-dose males when compared to the male controls. Pulmonary vascular mineralization was observed commonly in both control and test article-treated male and female rats; however, the FC-143-treated females displayed an increase that was inversely related to the dose.

The incidence of chronic sialadenitis, an inflammatory change of the salivary gland and often associated in rats with an antemortem viral infection, was increased in both the high- and low-dose males.

Hemosiderin, an iron rich pigment, was found in greater concentrations in the spleens of both high-dose males and females, but in greatly reduced amounts in the low-dose males and females as compared to controls.

Two changes observed in the gonads of both sexes, appeared to be related to the administration of FC-143. Vascular mineralization of the testes occurred in 18% of the high-dose males and 6% of the low-dose males, but was not seen in the controls. The incidence of testicular tubular atrophy was only slightly increased in the high-dose (22%) and low-dose (20%) males compared to the control males (14%).

In the test article-treated females, there was a dose-related, statistically significant increase in tubular hyperplasia of the ovarian stroma. Tubular hyperplasia is considered to be a diffuse, non-neoplastic increase in stromal tubular elements which is usually bilateral and associated with decreased or absent follicular development. The incidence

of this change was 0%, 32% and 14% in the control, high- and low-dose groups, respectively. Cystic glands of the uterine endometrium were found at a higher incidence in the low-dose females (24%) when compared to the controls (14%) and high-dose females (10%).

Other non-neoplastic lesions (Table 20) are commonly associated with either endemic diseases and/or geriatric changes found in this strain of rat. The following changes were considered equivocal test article-related findings or were usually decreased below the concurrent incidence in control rats. Adrenal changes are commonly seen in aging rats of this strain and the incidences were inconsistently either higher or lower than the control values. The incidence of sinusoidal ectasia (dilatation) was increased very slightly only in the high-dose males (32%) compared to the control males (22%), while the control and FC-143-treated females were almost equally affected (82 and 86%). The incidence of chronic myocarditis was reduced in an apparent dose-related fashion in the females while being increased above the control incidence in the high- and low-dose males. The incidence of thyroid C-cell hyperplasia was slightly increased in the high dose females, while only the low-dose males showed a similar change. The incidence of acinar atrophy of the pancreas was very slightly increased in the treated males, while being slightly depressed below control values in the high-dose female.

DISCUSSION

The purposes of this study was to define the long term toxicity and oncogenicity profile of FC-143, an anionic fluorochemical surfactant belonging to the chemical class of ammonium perfluoroalkyl carboxylates. The study was successfully completed with sufficient numbers of animals surviving in all of the experimental groups. The survival rates for the high-dose male and female rats were actually higher than those of the control rats after 24 months of the test.

The general health of a rat exposed to the experimental conditions of a 2 year feeding study may be examined at the beginning of the test by evaluating body weight gains and feed consumption compared to the study control animal population. Body weight gains of the FC-143-treated males decreased as early as the second week of the study, stabilized after 6 weeks, but remained slightly depressed in the high-dose males by at least 10% through 66 weeks. The treated females did not demonstrate any real decrease in body weight until the 18th month, so there appeared to be a rather obvious sex difference in this parameter. The body weight changes did not appear to be associated with the palatability of the diet admix since feed consumed on a body weight basis was actually increased. Further, since there was a modest dose-related effect seen in the male FC-143-treated rats, it appears that these body weight changes could be associated with a direct test article effect.

The concentration of the test article in the diet was within a 3% range of the proposed levels of 300 and 30 ppm for the full 2 years of the study. The average daily dose of FC-143 for the same time period and for both sexes combined, was estimated to be 15 and 1.5 mg/kg/day. Both in-life and postmortem results confirmed the systemic absorption of the test article and the 300 ppm dosage level appeared to adequately comply with the concept of a maximum tolerated dose for a long term study in this strain of rat.

The only clinical sign seen during the study which was associated with a test article effect was ataxia. The incidence of ataxia was increased in a dose related manner in the females, but not in the treated males. A

background incidence of this finding was seen in the male and female control population.

During the early course of the study, a decrease in red blood cell parameters was observed in the high-dose males. While these hematologic values were often decreased below the control male measurements at a statistically significant level ($p \leq 0.05$), generally the decreased values were still within the acceptable ranges for these parameters in the rat.

The elevation of serum alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase activities only in test article-treated male rats, suggested that FC-143 affected hepatocytes. These changes were seen from 3 to 18 months in both of the male FC-143-treatment groups, but only in the high-dose males at 24 months. These findings were substantiated by organ weight changes and histopathology observed at the 1 and 2 year sacrifices.

Changes in the character of the urine specimens were similar in both control and treated rats examined during the course of the study. These findings were considered to be associated with the slowly developing degenerative changes of naturally occurring chronic renal disease commonly found in rats of this strain.

The liver was the primary target organ affected as seen by an increase in relative organ weights, gross findings at necropsy, and histopathologic alterations. These changes seen at the 1 year necropsy showed remarkably little progression 1 year later. The FC-143-treated males were more obviously affected than the females. The sex differences seen in this study were consistent with earlier pharmacokinetic studies using carbon-14 labeled ammonium perfluorooctanoate, in which the females during 24 hours had excreted essentially 100% of an intravenous dose in the urine while the males excreted only 20%. Radioactive tissue residues were not detectable after 17 days in the females, while at 36 days, male rats had 2.8% of the carbon-14 in the liver, 1.1% in plasma, and lower but still detectable amounts in other organs.[1] Similar results were reported by Hanhijarvi, et al.[6]

Hepatomegalocytosis and hepatocellular vacuolation are characteristic of increased metabolic activity in the rat. Following chronic hepatic stimulation, evidence of cystoid degeneration and, occasionally, hepatocellular necrosis may also be observed. Since the liver in the rat rarely repairs parenchymal cell loss with fibrosis or scar tissue, the most common finding is hepatocellular hyperplasia. In this study, the incidence of hyperplastic nodules was increased very slightly in the high-dose group, but the incidence was not significantly different from controls. It is also important to note that no proliferative hepatic lesions (i.e. neither hyperplasia nor neoplasia) were seen in any of the high-dose rats receiving FC-143 for 1 year. The observed hepatomegalocytosis was similar to that reported by Pastoor et al in which perfluorooctanoic acid was administered orally to male rats at a higher dosage (50 mg/kg/day).[2] It was proposed that the hepatocytic enlargement was due to proliferation of smooth, endoplasmic reticulum, mitochondria, and peroxisomes.

The only hepatic neoplasms found in this study were hepatocellular carcinomas. The incidence of this tumor was 6%, 10% and 2% in the control, high- and low-dose male rats, respectively. Only one high-dose female was found to have this liver tumor. The incidence of hepatocellular carcinomas in high-dose males was not significantly greater than that of the control males and was comparable with the reported spontaneous incidence of this tumor.[3] Based on these findings, FC-143 was not considered to be a hepatic carcinogen in the rat.

The other neoplasms observed in this study originated from endocrine and/or endocrine sensitive organs; namely, the adrenal gland, mammary gland, pituitary gland, testes, and thyroid gland. The incidence for each of these tumors are presented in Table 19.

The incidence of mammary gland adenocarcinomas was 15%, 11% and 31% for the control, high- and low-dose female groups, respectively. While mammary gland carcinomas and adenomas were found only in the controls, there was an increased incidence of fibroadenomas in the high-dose (48%, statistically significant: $p \leq 0.05$), and the low-dose (42%) compared to controls (22%). It should also be noted that 2/13 of the high-dose females necropsied at 1

year were found to have fibroadenomas, while 0/15 of the controls were similarly affected. Although the incidence of fibroadenomas in high-dose females was significantly greater than that for the control females, the incidence was similar to that reported for untreated aging rats.[4] In addition, when the incidences for benign mammary gland tumors (adenoma and fibroadenoma) are combined, the tumor incidence in the high-dose group is no longer statistically significant.

Leydig cell adenomas (i.e. benign tumors of the testicular interstitial tissue), were found at an incidence of 0%, 14% and 4% in the control, high- and low-dose groups, respectively. The high-dose incidence for this lesion was statistically significant ($p \leq 0.05$) because the incidence in the control group was unusually low (0%). In addition, the spontaneous incidence reported for this neoplasm in this strain of rat was 7.4% for rats 24 to 29 months of age and was 14.6% at 30 to 38 months of age[3]. Based on another set of Sprague-Dawley two year study data compiled by Hazleton Laboratories, the spontaneous incidence of interstitial cell tumors was 28.7%.[5]

The remaining non-neoplastic findings reported from the histopathologic evaluation of all of the animals originally scheduled for the 2 year phase of the study were mostly geriatric lesions common to this strain of rat. The organs in which these lesions were found included: adrenal, heart, kidney, lung, testes, ovary, thyroid, urinary bladder and uterus. Specific deviations from control values seen in FC-143-treated groups were addressed in the results section of this report; however, the following changes may be considered incidental or equivocal test article-related effects.

The incidence of nodular hyperplasia of the adrenal cortex was increased (not statistically significant) in the high-dose males (18%) compared to the same finding in the controls (4%), while the high-dose females showed a much lower incidence (2%). Increases in the incidences of adrenal gland sinusoidal extasia (dilatation) were reported in the high- (32%) and low- (26%) dose males compared to male controls (22%) while the incidences in

all test article-treated females were equal to control values. It should be noted that adrenal lesions are commonly seen in old rats.

Thyroid C-cell hyperplasia was seen in the control males and FC-143-treated groups with an incidence of 10% and 7% for the low-dose males and the high-dose females, respectively. The incidences were not dose-related or statistically significant and were lower than the reported spontaneous incidence of this lesion.[3]

Chronic myocarditis (inflammation) was seen at a slightly higher incidence in the low-dose (36%) and the high-dose (34%) males compared to the control (28%) group. The female incidence for this lesion was 32%, 20% and 10% in the control, high- and low-dose groups, respectively. Inflammation of the heart is common in old rats. The lack of a true dose-related effect in either sex suggests that this finding is probably not a treatment related phenomenon.

Chronic renal histopathologic changes, commonly observed in aging rats, were not meaningfully altered by FC-143 treatment. None of these changes were apparently severe enough to produce pathologic lesions over a 2 year period. Therefore, none of these findings are considered to be directly related to treatment.

Lung changes which were seen more commonly in FC-143-treated rats than in controls included an increase in alveolar macrophages, pulmonary hemorrhage (agonal) and vascular mineralization. The first two lesions were seen predominantly in the high-dose males where the incidences were statistically significant ($p \leq 0.05$). Control males on the other hand, had higher incidences of interstitial pneumonia and pulmonary perivascular mononuclear cell infiltration. Pulmonary changes are common in aging rats.[3] Other than the possibility that an increase in the alveolar macrophages may be associated with FC-143 administration, all of the pulmonary changes were not considered related to test article treatment.

Chronic sialadenitis or inflammation of the salivary glands was significantly ($p \leq 0.05$) increased in the test article-treated males, but

not in the test article-treated females. These changes were attributed to outbreaks of sialodacryoadenitis viral infections which occurred in both the control and FC-143 animal rooms, but at different time periods and apparently with different levels of intensity.

The incidence of splenic hemosiderosis, depositions of iron-containing pigment in the sinusoids of the spleen, was increased above control levels by approximately 12% in only the high-dose males. However, the incidence in high-dose males was not significantly greater than the control incidence. The incidence of this lesion in FC-143 treated females was significantly lower than the incidence of splenic hemosiderosis in control females.

A statistically significant, dose-related increase in the incidences of ovarian (stromal) tubular hyperplasia was found in low and high-dose groups. The interpretation of these changes in the absence of any observable progressive pathologic lesion after 2 years of treatment, must be considered as equivocally related to FC-143 treatment.

CONCLUSIONS

The results obtained under the conditions of this study when FC-143 was administered in the diet of male and female rats at concentrations of 300 and 30 ppm for 2 years may be summarized as follows:

1. FC-143-related changes were found more commonly in males than in females of each of the two treatment groups. This finding supports earlier pharmacokinetic studies that demonstrated a increased FC-143 retention by treated males compared to treated female rats.

2. The major dose-related findings were observed in the liver and consisted of megalocytosis and cystoid degeneration with only a minimal proliferative response and related elevations of serum enzyme activities.

3. Other non-neoplastic findings reported in this study were not considered primary test article-related effects, but rather were related to spontaneous changes occurring in aging rats.

4. Based on the incidence, types of tumors, time of tumor appearance, malignancy patterns of tumors and survival rate after 2 years, FC-143 is not considered to be carcinogenic in the rat.

PRINCIPAL PERSONNEL INVOLVED WITH THE CONDUCT AND REPORTING OF RIKER EXPERIMENT NO. 0281CR0012 - TWO YEAR ORAL (DIET) TOXICITY/CARCINOGENICITY STUDY OF FLUOROCHEMICAL FC-143 IN RATS

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TWO YEAR ORAL (DIET) TOXICITY/CARCINOGENICITY STUDY OF FLUOROCHEMICAL FC-143 IN RATS

RIKER Experiment No. 0281CR0012

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Table 2 (concluded)

Two Year Oral (Diet) Toxicity-Oncogenicity Study
of Fluorocarbon FC-143 in Rats

Summary of Mean Body Weights (g) ± % Difference from Control

MALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
54	654.3	577.6	-11.7	641.9	- 1.9
56	661.6	583.1	-11.9	646.4	- 2.3
58	668.0	587.9	-12.0	652.7	- 2.3
60	673.2	590.8	-12.2	656.8	- 2.4
62	674.4	593.2	-12.0	655.7	- 2.8
64	664.5	596.8	-10.2	658.3	- 0.9
66	650.8	598.2	- 8.1	662.5	+ 1.8
68	656.6	604.9	- 7.9	666.5	+ 1.5
70	661.9	608.2	- 8.1	666.2	+ 0.6
72	658.3	608.5	- 7.6	664.4	+ 0.9
74	660.8	601.1	- 7.6	659.2	- 0.2
76	667.7	605.4	- 9.3	663.8	- 0.6
78	668.8	604.6	- 9.6	661.7	- 1.1
80	670.6	611.8	- 8.8	669.2	- 0.2
82	663.1	610.0	- 8.0	666.9	+ 0.6
84	668.1	617.5	- 7.6	662.3	- 0.9
86	675.6	617.4	- 8.6	664.5	- 1.6
88	678.9	614.7	- 9.5	654.7	- 3.6
90	690.0	624.6	- 9.5	662.4	- 4.0
92	686.0	621.8	- 9.4	652.9	- 4.8
94	678.3	627.6	- 7.5	660.0	- 2.7
96	677.5	621.0	- 8.3	653.4	- 3.6
98	675.7	627.2	- 7.2	659.7	- 2.4
100	671.1	625.5	- 6.8	660.0	- 1.7
102	665.9	629.4	- 5.5	664.0	- 0.3
104	642.0	613.3	- 4.5	650.8	+ 1.4

Table 3

Two Year Oral (Diet) Toxicity-Oncogenicity Study of Fluorocarbon FC-143 in Rats

Summary of Mean Body Weights (g) ± % Difference from Control

FEMALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
0	138.2	138.1	± 0.0	137.2	- 0.7
2	159.2	167.3	+ 5.1	166.0	+ 4.3
4	209.5	213.8	+ 2.1	214.9	+ 2.6
6	238.7	237.4	- 0.5	235.7	- 1.3
8	256.9	254.6	- 0.9	253.8	- 1.2
10	269.2	263.3	- 2.2	261.3	- 2.9
12	279.5	274.2	- 1.9	275.5	- 1.4
14	289.7	286.4	- 1.1	282.8	- 2.4
16	291.8	285.4	- 2.2	285.9	- 2.0
18	306.8	299.4	- 2.4	298.0	- 2.9
20	311.6	307.6	- 1.3	304.1	- 2.4
22	319.1	314.6	- 1.4	309.9	- 2.9
24	324.5	322.5	- 0.6	318.6	- 1.8
26	327.3	326.0	- 0.4	323.6	- 1.1
28	333.7	331.6	- 0.6	330.4	- 1.0
30	338.3	338.6	+ 0.1	339.0	+ 0.2
32	345.5	344.1	- 0.4	344.9	- 0.2
34	350.7	352.8	+ 0.6	353.5	+ 0.8
36	355.5	357.1	+ 0.5	358.0	+ 0.7
38	359.3	362.3	+ 0.8	363.1	+ 1.1
40	363.2	366.0	+ 0.8	367.5	+ 1.2
42	371.2	373.2	+ 0.5	375.9	+ 1.3
44	380.1	380.4	+ 0.1	382.0	+ 0.5
46	385.7	385.9	± 0.0	389.7	+ 1.0
48	392.3	391.6	- 0.2	395.8	+ 0.9
50	398.6	399.3	+ 0.2	399.7	+ 0.3
52	406.1	406.1	± 0.0	406.2	± 0.0

Table 3 (concluded)

Two Year Oral (Diet) Toxicity-Oncogenicity Study
of Fluorocarbon FC-143 in Rats

Summary of Mean Body Weights (g) ± % Difference from Control

FEMALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
54	414.1	411.5	- 0.6	412.6	- 0.4
56	419.1	421.2	+ 0.5	420.7	+ 0.4
58	420.9	426.4	+ 1.3	427.3	+ 1.5
60	423.6	427.0	+ 0.8	430.0	+ 1.5
62	426.6	431.9	+ 1.2	435.7	+ 2.1
64	426.1	434.0	+ 1.9	439.9	+ 3.2
66	424.9	435.5	+ 2.5	446.5	+ 5.1
68	427.5	433.0	+ 1.3	445.3	+ 4.2
70	431.4	429.1	- 0.5	443.5	+ 2.8
72	435.2	432.8	- 0.6	448.6	+ 3.1
74	446.5	444.6	- 0.4	463.3	+ 3.8
76	455.2	447.4	- 1.7	468.8	+ 3.0
78	464.8	452.7	- 2.6	471.3	+ 1.4
80	474.9	457.0	- 3.8	475.8	+ 0.2
82	484.0	461.8	- 4.6	485.7	+ 0.4
84	484.8	457.6	- 5.6	476.3	- 1.8
86	492.7	458.2	- 7.0	479.7	- 2.6
88	499.1	456.6	- 8.5	483.4	- 3.1
90	500.6	451.8	- 9.7	485.2	- 3.1
92	512.5	455.9	-11.0	486.3	- 5.1
94	505.7	451.0	-10.8	492.0	- 2.7
96	506.9	464.5	- 8.4	504.3	- 0.5
98	500.0	468.0	- 6.4	505.5	+ 1.1
100	501.2	464.2	- 7.4	505.6	+ 0.9
102	503.6	462.8	- 8.1	503.3	- 0.1
104	502.0	450.3	-10.3	501.8	± 0.0

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Table 4

Two Year Oral (Diet) Toxicity-Oncogenicity Study of Fluorocarbon FC-143 in Rats

Summary of Mean Food Consumption Per Kilogram Body Weight (g of diet consumed per day) ± % Difference from Control

MALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
1	102.0	98.6	- 3.3	103.8	+ 1.8
2	85.2	96.8	+13.6	85.0	- 0.2
4	76.4	84.0	+10.0	77.0	+ 0.8
6	69.4	67.7	- 2.5	61.2	-11.8
8	61.5	70.6	+14.8	64.1	+ 4.2
10	53.7	63.0	+17.3	57.4	+ 6.9
12	50.7	58.1	+14.6	51.3	+ 1.2
14	51.7	59.5	+15.1	53.5	+ 3.5
16	48.0	55.2	+15.0	49.3	+ 2.7
18	46.8	52.6	+12.4	47.7	+ 1.9
20	46.9	54.5	+16.2	48.9	+ 4.3
22	44.9	51.9	+15.6	47.3	+ 5.4
24	45.0	52.0	+15.6	46.3	+ 2.9
26	43.7	49.2	+12.6	44.9	+ 2.8
28	42.8	48.3	+12.9	44.5	+ 4.0
30	43.2	48.7	+12.7	43.7	+ 1.2
32	42.9	47.2	+10.0	44.0	+ 2.6
34	41.8	46.5	+11.2	42.8	+ 2.4
36	38.4	42.5	+10.7	39.7	+ 3.4
38	40.7	46.0	+13.0	42.2	+ 3.7
40	39.5	43.9	+11.1	41.8	+ 5.8
42	39.3	44.0	+12.0	41.3	+ 5.1
44	38.9	43.6	+12.1	40.5	+ 4.1
46	39.0	42.6	+ 9.2	39.7	+ 1.8
48	39.0	43.3	+11.0	38.9	- 0.3
50	38.5	43.2	+12.2	39.4	+ 2.3
52	36.5	41.1	+12.6	36.1	- 1.1

Table 4 (concluded)

Two Year Oral (Diet) Toxicity-Oncogenicity Study
of Fluorocarbon FC-143 in Rats

Summary of Mean Food Consumption Per Kilogram Body Weight
(g of diet consumed per day) ± % Difference from Control

MALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
54	37.0	42.2	+14.1	36.3	- 1.9
56	36.6	41.2	+12.6	37.9	+ 3.6
58	36.1	40.7	+12.7	37.5	+ 3.9
60	35.4	40.6	+14.7	37.3	+ 5.4
62	35.9	37.1	+ 3.3	37.1	+ 3.3
64	31.0	40.2	+29.7	34.5	+11.3
66	36.3	40.8	+12.4	36.4	+ 0.3
68	32.9	36.5	+10.9	33.5	+ 1.8
70	32.6	37.7	+15.6	33.0	+ 1.2
72	33.0	37.5	+13.6	34.9	+ 5.8
74	34.4	37.9	+10.2	36.7	+ 6.7
76	37.1	39.2	+ 5.7	36.9	- 0.5
78	36.6	39.7	+ 8.5	34.9	- 4.9
80	34.6	39.4	+13.9	36.8	+ 6.4
82	36.3	36.7	+ 1.1	37.6	+ 3.6
84	35.6	38.5	+ 8.2	34.3	- 3.7
86	35.1	38.6	+10.0	35.4	+ 0.9
88	34.8	33.0	- 5.2	33.0	- 5.2
90	34.9	36.3	+ 4.9	34.7	- 0.6
92	35.1	37.3	+ 6.3	35.1	± 0.0
94	38.5	40.5	+ 5.2	36.8	- 4.4
96	37.1	40.1	+ 8.1	37.5	+ 1.1
98	37.3	38.9	+ 4.3	37.4	+ 0.3
100	36.7	38.1	+ 3.8	37.3	+ 1.6
102	35.0	38.3	+ 9.4	37.2	+ 6.3
104	33.8	37.8	+11.8	37.5	+11.0

Table 5

Two Year Oral (Diet) Toxicity-Oncogenicity Study
of Fluorocarbon FC-143 in Rats

Summary of Mean Food Consumption Per Kilogram Body Weight
(g of diet consumed per day) ± % Difference from Control

FEMALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
1	98.8	96.6	- 2.2	96.1	- 2.7
2	107.0	101.6	- 5.1	103.0	- 3.7
4	97.2	81.8	-15.8	83.6	-14.0
6	81.0	81.1	+ 0.1	82.8	+ 2.2
8	74.1	74.9	+ 1.1	73.4	- 0.9
10	72.6	72.5	- 0.1	73.5	+ 1.2
12	70.2	70.4	+ 0.3	69.7	- 0.7
14	64.2	62.0	- 3.4	64.9	+ 1.1
16	57.2	56.3	- 1.6	58.8	+ 2.8
18	64.3	62.9	+ 2.2	64.6	+ 0.5
20	63.4	61.5	- 3.0	65.5	+ 3.3
22	58.6	61.2	+ 4.4	63.2	+ 7.9
24	59.5	58.0	- 2.5	61.2	+ 2.9
26	57.0	56.2	- 1.4	57.0	± 0.0
28	61.7	58.1	- 5.8	58.3	- 5.5
30	59.7	57.4	- 3.9	59.0	- 1.2
32	58.4	56.1	- 3.9	55.7	- 4.6
34	52.9	51.4	- 2.8	51.5	- 2.7
36	56.7	54.2	- 4.4	57.0	+ 0.5
38	56.8	52.7	- 7.2	54.3	- 4.4
40	58.4	51.6	-11.6	50.3	-13.9
42	54.2	53.6	- 1.1	52.9	- 2.4
44	54.7	51.8	- 5.3	53.9	- 1.5
46	48.5	50.8	+ 4.7	52.1	+ 7.4
48	49.2	50.3	+ 2.2	51.8	+ 5.3
50	51.4	45.1	-12.3	50.0	- 2.7
52	48.3	48.3	± 0.0	48.0	- 0.6

Table 5 (concluded)

Two Year Oral (Diet) Toxicity-Oncogenicity Study
of Fluorocarbon FC-143 in Rats

Summary of Mean Food Consumption Per Kilogram Body Weigh
(g of diet consumed per day) ± % Difference from Control

FEMALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
54	48.1	47.1	- 2.1	47.3	- 1.7
56	51.5	48.4	- 6.0	47.1	- 8.5
58	46.3	47.6	+ 2.8	46.3	± 0.0
60	49.6	49.2	- 0.8	47.7	- 3.8
62	47.1	46.5	- 1.3	44.8	- 4.9
64	48.4	46.1	- 4.8	44.1	- 8.9
66	41.0	39.5	- 3.7	39.6	- 3.4
68	44.9	41.3	- 8.0	39.8	-11.4
70	46.1	43.1	- 6.5	41.0	-11.1
72	45.3	44.1	- 2.7	44.4	- 2.0
74	48.4	45.9	- 5.2	44.5	- 8.1
76	48.3	45.8	- 5.2	44.4	- 8.1
78	44.1	44.0	- 0.2	43.7	- 0.9
80	45.7	44.4	- 2.8	38.5	-15.8
82	44.0	42.0	- 4.6	39.1	-11.1
84	43.5	39.8	- 8.5	38.2	-12.2
86	44.3	39.1	-11.7	37.7	-14.9
88	45.3	42.3	- 6.6	37.2	-21.8
90	46.1	45.6	- 1.1	38.5	-16.5
92	45.9	43.9	- 4.4	39.9	-13.1
94	46.9	47.5	+ 1.3	42.7	- 9.0
96	42.4	44.4	+ 4.7	37.7	-11.1
98	46.8	44.2	- 5.6	41.4	-11.5
100	41.5	44.0	+ 6.0	42.5	+ 2.4
102	42.5	46.2	+ 8.7	46.3	+ 8.9
104	41.6	50.9	+22.4	43.2	+ 3.9

EPA 02041

Table 6

Two Year Oral (Diet) Toxicity-Oncogenicity Study of Fluorocarbon FC-143 in Rats

Summary of Mean Food Consumption - Absolute (g/rat/day) ± % Difference from Control

MALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
1	22.2	18.7	-15.8	22.9	+ 3.2
2	23.1	22.7	- 1.7	23.0	- 0.4
4	25.5	23.2	- 9.0	25.3	- 0.8
6	27.1	20.9	-22.9	22.6	-16.6
8	26.4	24.9	- 5.7	26.3	- 0.4
10	24.5	24.0	- 2.0	25.4	+ 3.7
12	24.1	23.1	- 4.2	23.5	- 2.5
14	25.5	24.6	- 3.5	25.4	- 0.4
16	24.1	23.5	- 2.5	24.1	± 0.0
18	24.1	22.9	- 5.0	23.8	- 1.2
20	24.7	24.4	- 1.2	25.1	+ 1.6
22	24.3	23.7	- 2.5	24.6	+ 1.2
24	24.8	24.1	- 2.8	24.4	- 1.6
26	24.5	23.4	- 4.5	24.2	- 1.2
28	24.3	23.4	- 3.7	24.3	± 0.0
30	24.9	24.2	- 2.8	24.4	- 2.0
32	24.9	23.9	- 4.0	24.9	± 0.0
34	24.3	23.8	- 2.1	24.5	+ 0.8
36	22.7	21.9	- 3.5	22.8	+ 0.4
38	24.4	24.1	- 1.2	24.7	+ 1.2
40	24.0	23.5	- 2.1	24.8	+ 3.3
42	24.1	23.8	- 1.2	24.8	+ 2.9
44	24.1	24.0	- 0.4	24.7	+ 2.5
46	24.3	23.5	- 3.3	24.3	± 0.0
48	24.4	24.2	- 0.8	24.1	- 1.2
50	24.6	24.5	- 0.4	24.7	+ 0.4
52	23.3	23.4	+ 0.4	22.9	- 1.7

Table 6

Two Year Oral (Diet) Toxicity-Oncogenicity Study of Fluorocarbon FC-143 in Rats

Summary of Mean Food Consumption - Absolute (g/rat/day) ± % Difference from Control

MALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
54	24.2	24.4	+ 0.8	23.3	- 3.7
56	24.2	24.0	- 0.8	24.5	+ 1.2
58	24.1	23.9	- 0.8	24.5	+ 1.7
60	23.8	24.0	+ 0.8	24.5	+ 2.9
62	24.2	22.0	- 9.1	24.3	+ 0.4
64	20.6	24.0	+16.5	22.7	+10.2
66	23.6	24.4	+ 3.4	24.1	+ 2.1
68	21.6	22.1	+ 2.3	22.3	+ 3.2
70	21.6	22.9	+ 6.0	22.0	+ 1.9
72	21.7	22.8	+ 5.1	23.2	+ 6.9
74	22.7	22.8	+ 0.4	24.2	+ 6.6
76	24.8	23.7	- 4.4	24.5	- 1.2
78	24.5	24.0	- 2.0	23.1	- 5.7
80	23.2	24.1	+ 3.9	24.6	+ 6.0
82	24.1	22.4	- 7.1	25.1	+ 4.2
84	23.8	23.8	± 0.0	22.7	- 4.6
86	23.7	23.8	+ 0.4	23.5	- 0.8
88	23.6	20.3	-14.0	21.6	- 8.5
90	24.1	22.7	- 5.8	23.0	- 4.6
92	24.1	23.2	- 3.7	22.9	- 5.0
94	26.1	25.4	- 2.7	24.3	- 6.9
96	25.1	24.9	- 0.8	24.5	- 2.4
98	25.2	24.4	- 3.2	24.7	- 2.0
100	24.6	23.8	- 3.3	24.6	± 0.0
102	23.3	24.1	+ 3.4	24.7	+ 6.0
104	21.7	23.2	+ 6.9	24.4	+12.4

EPA 02043

Table 7

Two Year Oral (Diet) Toxicity-Oncogenicity Study
of Fluorocarbon FC-143 in Rats

Summary of Mean Food Consumption - Absolute
(g/rat/day) ± % Difference from Control

FEMALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
1	13.5	13.5	± 0.0	13.3	- 1.5
2	17.0	17.0	± 0.0	17.1	+ 0.6
4	20.4	17.5	-14.2	18.0	-11.8
6	19.3	19.2	- 0.5	19.5	+ 1.0
8	19.0	19.1	+ 0.5	18.6	- 2.1
10	19.5	19.1	- 2.1	19.2	- 1.5
12	19.6	19.3	- 1.5	19.2	- 2.0
14	18.6	17.8	- 4.3	18.4	- 1.1
16	16.7	16.1	- 3.6	16.8	+ 0.6
18	19.7	18.8	- 4.6	19.3	- 2.0
20	19.8	18.9	- 4.6	19.9	+ 0.5
22	18.7	19.2	+ 2.7	19.6	+ 4.8
24	19.3	18.7	- 3.1	19.5	+ 1.0
26	18.7	18.3	- 2.1	18.4	- 1.6
28	20.6	19.3	- 6.3	19.3	- 6.3
30	20.2	19.4	- 4.0	20.0	- 1.0
32	20.2	19.3	- 4.5	19.2	- 5.0
34	18.5	18.1	- 2.2	18.2	- 1.6
36	20.2	19.4	- 4.0	20.4	+ 1.0
38	20.4	19.1	- 6.4	19.7	- 3.4
40	21.2	18.9	-10.9	18.5	-12.7
42	20.1	20.0	- 0.5	19.9	- 1.0
44	20.8	19.7	- 5.3	20.6	- 1.0
46	18.7	19.6	+ 4.8	20.3	+ 8.6
48	19.3	19.7	+ 2.1	20.5	+ 6.2
50	20.5	18.0	-12.2	20.0	- 2.4
52	19.6	19.6	± 0.0	19.5	- 0.5

Table 7

Two Year Oral (Diet) Toxicity-Oncogenicity Study
of Fluorocarbon FC-143 in Rats

Summary of Mean Food Consumption - Absolute
(g/rat/day) ± % Difference from Control

FEMALES

Study Week	Control Mean Wt.	300 ppm Mean Wt.	% Diff.	30 ppm Mean Wt.	% Diff.
54	19.9	19.4	- 2.5	19.5	- 2.0
56	21.6	20.4	- 5.6	19.8	- 8.3
58	19.5	20.3	+ 4.1	19.8	+ 1.5
60	21.0	21.0	± 0.0	20.5	- 2.4
62	20.1	20.1	± 0.0	19.5	- 3.0
64	20.6	20.0	- 2.9	19.4	- 5.8
66	17.4	17.2	- 1.2	17.7	+ 1.7
68	19.2	17.9	- 6.8	17.7	- 7.8
70	19.9	18.5	- 7.0	18.2	- 8.5
72	19.7	19.1	- 3.1	19.9	+ 1.0
74	21.6	20.4	- 5.6	20.6	- 4.6
76	22.0	20.5	- 6.8	20.8	- 5.5
78	20.5	19.9	- 2.9	20.6	+ 0.5
80	21.7	20.3	- 6.5	18.3	-15.7
82	21.3	19.4	- 8.9	19.0	-10.8
84	21.1	18.2	-13.7	18.2	-13.7
86	21.8	17.9	-17.9	18.1	-17.0
88	22.6	19.3	-14.6	18.0	-20.4
90	23.1	20.6	-10.8	18.7	-19.1
92	23.5	20.0	-14.9	19.4	-17.5
94	23.7	21.4	- 9.7	21.0	-11.4
96	21.5	20.6	- 4.2	19.0	-11.6
98	23.4	20.7	-11.5	20.9	-10.7
100	20.8	20.4	- 1.9	21.5	+ 3.4
102	21.4	21.4	± 0.0	23.3	+ 8.9
104	20.9	22.9	+ 9.6	21.7	+ 3.8

TABLE 8

Estimated Mean FC-143 (mg/kg Body Weight)

Consumption Per Day

Study Week	300 ppm		30 ppm	
	Male	Female	Male	Female
1	29.6	29.0	3.1	2.9
2	29.0	30.5	2.6	3.1
4	25.2	24.5	2.3	2.5
6	20.3	24.3	1.8	2.5
8	21.2	22.5	1.9	2.2
10	18.9	21.8	1.7	2.2
12	17.5	21.1	1.5	2.1
14	17.9	18.6	1.6	2.0
16	16.6	16.9	1.5	1.8
18	15.8	18.9	1.4	1.9
20	16.4	18.4	1.5	2.0
22	15.6	18.3	1.4	1.9
24	15.6	17.4	1.4	1.8
26	14.8	16.9	1.4	1.7
28	14.5	17.4	1.3	1.8
30	14.6	17.2	1.3	1.8
32	14.2	16.8	1.3	1.7
34	13.9	15.4	1.3	1.6
36	12.8	16.3	1.2	1.7
38	13.8	15.8	1.3	1.6
40	13.2	15.5	1.3	1.5
42	13.2	16.1	1.2	1.6
44	13.1	15.5	1.2	1.6
46	12.8	15.2	1.2	1.6
48	13.0	15.1	1.2	1.5
50	13.0	13.5	1.2	1.5
52	12.3	14.5	1.1	1.4

TABLE 8 (Continued)

Estimated Mean FC-143 (mg/kg Body Weight)

Consumption Per Day

Study Week	300 ppm Male	300 ppm Female	30 ppm Male	30 ppm Female
54	12.7	14.1	1.1	1.4
56	12.4	14.5	1.1	1.4
58	12.2	14.3	1.1	1.4
60	12.2	14.8	1.1	1.4
62	11.1	14.0	1.1	1.3
64	12.1	13.8	1.0	1.3
66	12.2	11.9	1.1	1.2
68	11.0	12.4	1.0	1.2
70	11.3	12.9	1.0	1.2
72	11.2	13.2	1.1	1.3
74	11.4	13.8	1.1	1.3
76	11.7	13.8	1.1	1.3
78	11.9	13.2	1.1	1.3
80	11.8	13.3	1.1	1.2
82	11.0	12.6	1.1	1.2
84	11.6	11.9	1.0	1.2
86	11.6	11.7	1.1	1.1
88	9.9	12.7	1.0	1.1
90	10.9	13.7	1.0	1.2
92	11.2	13.2	1.1	1.2
94	12.1	14.2	1.1	1.3
96	12.0	13.3	1.1	1.1
98	11.7	13.3	1.1	1.2
100	11.4	13.2	1.1	1.3
102	11.5	13.9	1.1	1.4
104	11.4	15.3	1.1	1.3

TABLE 9

TWO YEAR ORAL (DIET) TOXICITY-ONCOGENICITY STUDY OF FLUOROCARBON FC-143 IN RATS
MORTALITY DATA

DOSE GROUP	INITIAL NO.	WEEK OF STUDY 1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36	37-40	41-44	45-48	49-52	53-56
MALES															
CONTROL 0 PPM	50	0	0	0	0	0	0	0	0	1	0	0	0	0	1
HIGH DOSE 300 PPM	50	0	0	0	0	1	0	1	0	0	0	0	0	0	0
LOW DOSE 30 PPM	50	0	0	0	0	0	0	0	0	0	1	0	0	0	0
FEMALES															
CONTROL 0 PPM	50	0	0	0	0	0	0	1	0	0	1	0	0	1	1
HIGH DOSE 300 PPM	50	0	0	0	0	0	0	0	0	0	0	0	0	1	1
LOW DOSE 30 PPM	50	0	0	0	0	0	0	0	0	0	0	1	1	1	0

TABLE 9

TWO YEAR ORAL (DIET) TOXICITY-ONCOGENICITY STUDY OF FLUOROCARBON FC-143 IN RATS
MORTALITY DATA

DOSE GROUP	INITIAL NO.	WEEK OF STUDY 57-60	61-64	65-68	69-72	73-76	77-80	81-84	85-88	89-92	93-96	97-100	101-104	105-108	1-109 WEEK TOTALS NO.	%
MALES																
CONTROL 0 PPM	50	0	1	0	0	1	0	1	4	1	2	1	2	1	16	32
HIGH DOSE 300 PPM	50	0	0	0	2	0	0	0	0	1	0	1	0	0	6	12
LOW DOSE 30 PPM	50	0	0	2	2	0	0	0	1	1	4	1	2	0	14	28
FEMALES																
CONTROL 0 PPM	50	0	3	0	0	1	3	2	2	1	3	5	1	0	25	50
HIGH DOSE 300 PPM	50	1	1	0	0	1	2	1	3	1	4	2	3	0	21	42
LOW DOSE 30 PPM	50	0	0	0	1	1	0	5	1	1	6	7	1	0	26	52

CHI-SQUARE TESTS FOR DOSE GROUP DIFFERENCES FROM CONTROL

DOSE GROUP	MALES CHI-SQUARE	MALES PROB.	FEMALES CHI-SQUARE	FEMALES PROB.
300 PPM	* 4.72	0.029	0.36	0.555
30 PPM	0.05	0.411	0.00	1.000

* Significant difference from control at the 5% level

Table 10

Two Year Oral (Diet) Toxicity - Oncogenicity Study of Fluorocarbon FC-143 in Rats

Summary of Clinical Observations

	Control			300 ppm			30 ppm		
	M	F	%[a]	M	F	%[a]	M	F	%[a]
Initial number of rats	65	65	100.0	65	65	100.0	50	50	100.0
Survivors at end of study	34	25	45.4	44	29	56.2	36	24	60.0
Mass(es)[b] in various areas	19	38	43.8	10	40	38.5	7	41	48.0
(Mass[es] resolved prior to term)	(11)	(7)	(13.9)	(8)	(7)	(11.5)	(4)	(5)	(9.0)
Alopecia in various areas	6	14	15.4	9	16	19.2	6	16	22.0
Swollen throat[c]	13	10	15.4	2	9	8.5	4	8	12.0
Pale (blanched) eyes and/or appears thin (emaciated)	9	9	13.9	5	8	10.0	9	10	19.0
Excessive lacrimation	8	12	15.4	9	7	12.3	8	5	13.0
Ataxia	4	2	4.6	2	15	13.1	5	9	14.0
Convulsions (clonic)	3	0	2.3	2	0	1.5	4	0	4.0
Occasional urinary incontinence and/or hematuria	5	4	6.9	1	2	2.3	3	4	7.0
Raised ulcerated lesion on hind foot pad(s)	7	0	5.4	1	1	1.5	5	0	5.0
Occasional bloody nares	3	1	3.0	0	6	4.6	0	1	1.0

[a] (Incidence in males + incidence in females) /total number of animals in the group x 100
[b] To be detailed in the pathology report
[c] Indication of Sialodacryoadenitis (SDA) viral infection

Table 10

Two Year Oral (Diet) Toxicity - Oncogenicity Study of Fluorocarbon FC-143 in Rats

Summary of Clinical Observations

	Control		500 ppm		30 ppm	
	M	F	M	F	M	F
Occasional bloody feces and/or diarrhea	2	0	2	1	1	0
Occasional episode of dyspnea	1	0	1	0	0	0
Listing of the head	1	0	0	5	1	2
Circular ulcerated area on skin	4	3	1	0	1	0
Swollen (distended) abdomen	0	2	2	0	0	2
Swelling in inguinal area	1	1	0	0	0	0
Swollen leg and/or foot	3	0	2	1	1	0
Swollen ears	0	0	0	1	0	1
Swollen penis	0	-	0	-	1	-
Paresis of hind leg(s)/feet	1	0	1	0	2	0

Table 11

Two Year Oral (Diet) Toxicity - Oncogenicity Study of Fluorocarbon FC-143 in Rats

Summary of Clinical Ophthalmologic Findings

Observations	Eye(s)	Control - 0 ppm		300 ppm		30 ppm	
		M	F	M	F	M	F
Phthisis Bulbi (Atrophy)	Right	0	1	3	3	1	3
	Left	0	1	0	0	0	0
Posterior Subcapsular Cateract(s)	Right	2	0	1	0	0	0
	Left	2	1	1	0	0	0
	Bilateral	1	0	0	0	0	0
Corneal (ocular) Opacity (Diffused; ulcerated; focal with iris staphyloma; with pannus; partially collapsed).	Right	0	2	0	0	2	0
	Left	0	2	0	0	2	0
	Bilateral	0	1	0	0	0	0
Chronic superficial Keratitis	Right	0	1	2	0	0	0
	Bilateral	1	0	2	0	0	0

Note: Blood samples were taken via the retro-orbital venus plexus from almost all of the above animals with ophthalmologic abnormalities.

Table 11

Two Year Oral (Diet) Toxicity - Oncogenicity Study of Fluorocarbon FC-143 in Rats

Summary of Clinical Ophthalmologic Findings

(M) Group	Eye(s)	Description of Abnormality
Males		
(1) Control	Right	Chronic uveitis (secondary to blood sampling)
(1) Control	Right	Diffused lens opacity and chronic iritis with microphthalmos
(1) Control	Bilateral	Posterior lens opacity
(1) Control	Bilateral	Very pale choroidal circulation
(1) High dose	Right	Dacryadenitis
(1) High dose	Bilateral	Chronic uveitis with anterior synechia in right eye
(1) High dose	Bilateral	Diffused lens opacity
(1) High dose	Left	Focal, posterior, capsul lens opacity
Females		
(1) Control	Left	Chronic uveitis with secondary exophthalmia
(1) Control	Right	Dacryadenitis
(1) Low dose	Left	Diffused lens opacity with pannus and microphthalmia

TABLE 12

TWO YEAR ORAL (DIET) TOXICITY-ONCOGENICITY STUDY OF FLUOROCARBON FC-143 IN RATS
MEAN ERYTHROCYTE VALUES WITH STANDARD DEVIATIONS

		ERYTHROCYTES (CELLS X 10**6)		HEMOGLOBIN (G/DL)		HEMATOCRIT (% PACKED CELLS)		MCV (MICRONS**3)		MCH (PICOGRAMS)		MCHC (%)	
	N	MEAN	S.DEV.	MEAN	S.DEV.	MEAN	S.DEV.	MEAN	S.DEV.	MEAN	S.DEV.	MEAN	S.DEV.
MALE													
MONTH 3													
0 PPM	15	8.29	0.322	16.4	0.39	45.9	0.96	55	1.9	19.8	0.80	35.4	0.41
300 PPM	15	7.91	0.743	15.5*	0.50	43.3*	1.10	55	4.3	19.7	1.55	35.8	0.45
30 PPM	15	7.87	0.475	16.1	0.67	44.5*	1.92	57	2.5	20.5	0.83	36.2*	0.55
MONTH 6													
0 PPM	15	8.42	0.384	15.1	0.94	44.5	2.70	58	4.3	17.9	1.41	33.9	0.71
300 PPM	15	7.91*	0.350	14.5	1.01	43.1	1.64	56	3.0	18.4	1.34	33.7	1.93
30 PPM	15	7.58*	0.306	14.8	0.83	43.9	2.39	58*	1.9	19.6*	0.79	33.8	1.82
MONTH 12													
0 PPM	14	8.44	0.554	15.9	1.17	46.7	3.69	55	2.2	18.8	0.84	34.0	0.91
300 PPM	15	8.01*	0.473	15.2	0.70	42.7*	1.98	53*	1.7	19.0	0.54	35.7*	0.76
30 PPM	15	8.38	0.354	15.5	0.52	44.5	1.88	53*	1.2	18.5	0.72	34.8*	0.99
MONTH 18													
0 PPM	15	7.48	2.071	15.1	3.12	40.8	9.14	56	6.2	21.0	3.09	37.2	1.51
300 PPM	15	7.55#	0.635	14.8#	1.15	40.6#	3.00	54	2.2	19.6	0.92	36.4	0.81
30 PPM	15	8.42	1.106	15.8	1.52	46.1#	4.41	54	4.6	18.4#	0.93	34.3*	1.01
MONTH 24													
0 PPM	15	7.84	1.083	14.5	1.59	42.3	5.34	54	3.4	18.6	1.27	34.4	0.81
300 PPM	15	7.92	0.670	14.6	1.42	43.3	5.72	55	5.6	18.4	1.10	33.8	1.71
30 PPM	14	7.95	0.869	14.7	1.23	42.5	4.22	54	2.8	18.5	0.91	34.6	0.78

* : P <= .05. TWO TAILED DUNNETT T ON RAW DATA.
\# : P <= .05. TWO TAILED DUNNETT T ON RANKED DATA.

TABLE 12

TWO YEAR ORAL (DIET) TOXICITY-ONCOGENICITY STUDY OF FLUOROCARBON FC-143 IN RATS
MEAN LEUKOCYTE VALUES WITH STANDARD DEVIATIONS

		LEUKOCYTES (CELLS X 10**3)		NEUTROPHILS (CELLS X 10**3)		LYMPHOCYTES (CELLS X 10**3)		MONOCYTES (CELLS X 10**3)		EOSINOPHILS (CELLS X 10**3)	
	N	MEAN	S.DEV.	MEAN	S.DEV.	MEAN	S.DEV.	MEAN	S.DEV.	MEAN	S.DEV.
MALE											
MONTH 3											
0 PPM	15	12.73	2.074	1.65	0.656	10.72	1.803	0.18	0.196	0.17	0.136
300 PPM	15	14.93	2.801	1.58	0.936	13.08*	2.206	0.10	0.102	0.16	0.178
30 PPM	15	15.22*	3.052	2.14	0.870	12.83*	2.861	0.17	0.173	0.11	0.157
MONTH 6											
0 PPM	15	10.74	2.423	1.43	0.727	8.85	2.416	0.29	0.180	0.17	0.121
300 PPM	15	12.72	2.160	1.99	0.989	10.06	2.316	0.38	0.154	0.20	0.227
30 PPM	15	14.46*	3.223	1.92	1.146	11.81*	2.978	0.33	0.235	0.31	0.362
MONTH 12											
0 PPM	14	7.94	1.572	1.10	0.612	6.35	1.256	0.48	0.216	0.10	0.107
300 PPM	15	8.14	1.789	2.26*	0.656	5.36	1.246	0.39	0.247	0.14	0.105
30 PPM	15	10.38*	1.747	2.21*	1.346	7.56	2.151	0.44	0.233	0.18	0.117
MONTH 18											
0 PPM	15	11.41	7.325	5.06	6.402	5.61	1.504	0.59	0.405	0.16	0.128
300 PPM	15	9.91	1.479	2.78	1.657	6.30	1.070	0.63	0.294	0.20	0.156
30 PPM	15	11.16	5.157	2.55#	3.353	8.20*	2.568	0.30*	0.190	0.11	0.163
MONTH 24											
0 PPM	15	10.79	7.529	3.72	5.666	6.66	2.140	0.34	0.398	0.08	0.083
300 PPM	15	9.09	2.351	2.41	1.488	6.34	1.619	0.26	0.176	0.08	0.109
30 PPM	14	10.44	3.464	3.24	2.032	6.72	2.171	0.39	0.292	0.09	0.106

* : P <= .05. TWO TAILED DUNNETT T ON RAW DATA.
# : P <= .05. TWO TAILED DUNNETT T ON RANKED DATA.

TABLE 12

TWO YEAR ORAL (DIET) TOXICITY-ONCOGENICITY
STUDY OF FLUOROCARBON FC-143 IN MALE RATS
INDIVIDUAL HEMOGRAM VALUES

MONTH=3

DOSE	ANIMAL	ERYTH	HEMO	HEMAT	MCV	MCH	MCHC	WBC	PMNAB	LYMAB	MONOAB	EOSAB
0 PPM	A1R3518	8.10	16.1	45	55.5556	19.8765	35.7778	12.60	1.3860	10.9620	0.000	0.252
0 PPM	A1R3527	7.77	15.5	44	56.6281	19.9485	35.2273	11.00	1.6500	9.0200	0.110	0.220
0 PPM	A1R3532	8.69	16.5	46	52.9344	18.9873	35.8696	10.00	1.0000	8.9000	0.000	0.100
0 PPM	A1R3534	8.15	16.3	45	55.2147	20.0000	36.2222	13.30	1.3300	11.5710	0.266	0.133
0 PPM	A1R3537	7.71	16.3	45	58.3058	21.1414	36.2222	11.30	2.4860	8.8140	0.000	0.000
0 PPM	A1R3540	8.04	16.7	46	57.2139	20.7711	36.3043	12.50	1.8750	9.8750	0.250	0.500
0 PPM	A1R3542	8.70	16.8	47	54.0230	19.3103	35.7447	12.60	1.3860	10.9620	0.252	0.000
0 PPM	A1R3548	8.13	16.5	47	57.8106	20.2952	35.1064	15.50	2.6350	12.0900	0.620	0.155
0 PPM	A1R3552	8.20	16.6	46	56.0976	20.2439	36.0870	14	1.9600	11.4800	0.280	0.280
0 PPM	A1R3559	8.63	16.4	46	53.3024	19.0035	35.6522	1	350	10.1200	0.000	0.345
0 PPM	A1R3562	8.73	15.6	45	51.5464	17.8694	34.6667		510	9.4010	0.119	0.119
0 PPM	A1R3564	8.37	16.6	47	56.1529	19.8327	35.3191		3860	10.8360	0.252	0.126
0 PPM	A1R3565	8.41	16.3	46	54.6966	19.3817	35.4348	9.20	0.7664	8.8136	0.000	0.000
0 PPM	A1R3567	8.24	16.8	47	57.0388	20.3883	35.7447	15.50	2.7900	12.5550	0.000	0.155
0 PPM	A1R3569	8.46	16.6	47	55.5556	19.6217	35.3191	17.00	0.8500	15.4700	0.510	0.170
300 PPM	B1R3585	7.33	15.0	42	57.2988	20.4638	35.7143	14.20	1.1360	13.0640	0.000	0.000
300 PPM	B1R3587	7.83	16.0	44	56.1941	20.4342	36.3636	14.30	1.7160	12.4410	0.000	0.143
300 PPM	B1R3589	7.67	15.1	43	56.0626	19.6671	35.1163	13.40	1.0720	11.9260	0.268	0.134
300 PPM	B1R3592	7.73	15.0	43	55.6274	19.4049	34.8837	19.60	2.1560	17.2480	0.000	0.196
300 PPM	B1R3593	6.09	14.7	41	67.3235	24.1379	35.8537	10.70	0.5350	10.0580	0.107	0.000
300 PPM	B1R3595	7.81	15.5	43	55.0576	19.8464	36.0465	13.90	1.2510	12.3710	0.139	0.139
300 PPM	B1R3604	7.77	14.8	42	54.0541	19.0476	35.2381	14.00	0.4200	13.3000	0.000	0.280
300 PPM	B1R3605	7.64	15.4	43	56.2827	20.1571	35.8140	15.20	2.1280	12.9200	0.000	0.152
300 PPM	B1R3610	7.99	15.5	43	53.8173	19.3492	36.0465	21.70	3.6890	17.7940	0.217	0.000
300 PPM	B1R3611	8.27	15.9	44	53.2044	19.2261	36.1364	17.90	1.9690	15.3940	0.000	0.537
300 PPM	B1R3617	7.70	16.0	44	57.1429	20.7792	36.3636	14.40	3.0240	11.0880	0.288	0.000
300 PPM	B1R3623	9.02	16.0	45	49.8891	17.7384	35.5556	13.50	1.3500	11.6100	0.135	0.405
300 PPM	B1R3634	8.15	15.8	44	53.9877	19.3865	35.9091	14.70	0.5880	13.9650	0.147	0.000
300 PPM	B1R3640	8.17	15.5	43	52.6316	18.9718	36.0465	12.20	0.7320	11.3460	0.122	0.000
300 PPM	B1R3643	9.44	16.3	45	47.6695	17.2669	36.2222	14.30	2.0020	11.7260	0.143	0.429
30 PPM	C1R3654	7.10	15.6	43	60.5634	21.9718	36.2791	16.40	2.2960	13.9400	0.164	0.800
30 PPM	C1R3655	7.85	15.7	42	53.5032	20.0000	37.3810	10.40	0.5200	9.8800	0.000	0.000
30 PPM	C1R3665	7.77	15.8	43	55.3411	20.3346	36.7442	12.70	2.1590	10.5410	0.000	0.000
30 PPM	C1R3667	7.88	16.5	45	57.1066	20.9391	36.6667	14.70	2.3520	11.7600	0.441	0.147
30 PPM	C1R3668	8.31	17.0	46	55.3550	20.4573	36.9565	11.50	2.4150	8.7400	0.345	0.000
30 PPM	C1R3673	8.27	16.0	44	53.2044	19.3470	36.3636	15.10	2.5670	12.3620	0.151	0.000
30 PPM	C1R3675	7.30	15.0	42	57.5342	20.5479	35.7143	17.00	3.4000	12.7500	0.510	0.340
30 PPM	C1R3677	8.58	16.5	46	53.6131	19.2308	35.8696	14.50	2.3200	12.0350	0.000	0.145
30 PPM	C1R3679	8.41	16.6	46	54.6968	19.7146	36.0870	20.80	2.2880	18.5120	0.208	0.208
30 PPM	C1R3683	7.83	16.5	46	58.7484	21.0728	35.8696	17.20	1.7200	15.4800	0.000	0.000
30 PPM	C1R3687	8.37	17.6	49	58.5924	21.0275	35.9184	15.70	0.9420	14.6010	0.157	0.000
30 PPM	C1R3690	7.03	15.5	43	61.1664	22.0484	36.0465	14.40	1.3320	13.0240	0.296	0.148
30 PPM	C1R3691	7.90	15.8	45	56.9620	20.0000	35.1111	21.30	3.4080	17.8920	0.000	0.000
30 PPM	C1R3692	7.91	16.0	44	55.6258	20.2276	36.3636	13.40	3.2160	9.6480	0.000	0.536
30 PPM	C1R3695	7.52	15.6	43	57.1809	20.7447	36.2791	12.40	1.1520	11.2640	0.256	0.128